REMARKS

The present communication is responsive to the Official Action of October 14, 2005. Claims 4, 6, 7, 9-12, 16-26, 33, 37, and 38 presently appear in this case. Claims 16-26 and 37 have been withdrawn from consideration. Claims 6 and 7 have been rejected only because they depend from a claim which is subject to a 35 USC §112 rejection. They have not been rejected over the prior art and the language of these claims is not subject to the grounds for the 35 USC §112 rejections of the claim from which it depends. Accordingly, it is still believed that these claims are allowable if rewritten into independent form. The remaining claims under consideration have been rejected. The Official Action of October 14, 2005, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly the present invention relates to chimeric glycosylated soluble interleukin-6 receptor (sIL-6R)-interleukin-6 (IL-6) polypeptides constructed from the fusion of the naturally occurring sequences of sIL-6RδVal and IL-6, with a linker of 3-4 amino acids therebetween or the 13 amino acid linker of SEQ ID NO: 1 therebetween, which linkers do not prevent the chimeric polypeptide from triggering dimerization of gp130 in human cells. The invention also relates to DNA encoding same, vectors made from said DNA, and methods of

making such polypeptides. The present invention is also related to pharmaceutical compositions containing such polypeptides and methods of use for the treatment of cancer and liver disorders, enhancement of bone marrow transplantation, and treatment of other IL-6 related conditions.

Claims 4, 6, 7, 9-11, 33 and 38 have been rejected under 35 USC §112, second paragraph, as being indefinite. The Examiner states that claim 38 is indefinite because it recites sIL-6R-δVal-IL-6. The Examiner states that this term is never defined in a limiting fashion in the present specification and that one of ordinary skill in the art does not know what it means in the absence of a clear definition. The Examiner considers the use of the Greek letter delta to be confusing as it is normally used to indicate that certain residues have been deleted. The Examiner states that at page 8, lines 3-6, the delta character appears to be used when an amino acid sequence is added. The Examiner also considers claim 38 to be indefinite because the preamble is drawn to a chimeric sIL-6R/IL-6 polypeptide, but the body of the claim recites sIL-6RδVal fused to IL-6. The Exmainer does not know whether the genus of sIL-6R is coextensive with sIL-6RδVal or whether the former is a broader genus than the latter. This rejection is respectfully traversed.

One of ordinary skill in the art reading the present specification and drawings would have no trouble understanding the meaning of sIL-6RδVal as used in the present specification. Specifically, the Examiner's attention is invited to the paragraph beginning on page 8, line 3, of the present specification. This paragraph states that an example of a chimeric sIL-6R/IL-6 protein is the herein designated sIL-6RδVal/IL-6 having a tripeptide linker between the C-terminal Val-356 of sIL-6R and the N-terminal Pro-29 of IL-6, which chimeric protein has the sequence set forth in Figure 3. This indicates that the linker is not part of the sIL-6RδVal and that the sIL-6RδVal part of the chimeric protein ends at Val-356 and the IL-6 part of the chimeric protein begins at Pro-29. Thus, sIL-6RδVal is clearly defined as the sequence from 1 - 356, shown in Figure 3. This is also consistent with the explanation in the paragraph beginning at page 8, line 7.

It should be noted that the latter paragraph has been corrected by the present amendment because two obvious errors were noted therein. Pro-29 is clearly the N-terminal of IL-6, not IL-6R (see the description of Figure 3 beginning at page 13, line 7, where the underlined portion beginning at Pro-360 is defined as the mature IL-6 moeity of the chimera). Note also the correct statement at page 8, line 5, that Pro-29 in the N-terminal of IL-6. In the penultimate line of the

paragraph, "between" has been changed to --at-- as EFM is obviously at these positions, not between them, as is clearly seen in Figure 3.

The definition of sIL-6RδVal discussed above is consistent with the description of Figure 3, beginning at page 13, line 7, and the description of Figure 11, beginning at page 15, line 1, which also refers to the sIL-6RδVal and shows its sequence, which ends with the same valine at residue 471 of Figure 11 as is shown at residue 356 in Figure 3. The description at page 29, line 23-27 is also consistent where it speaks of the C-terminal Val-356 of the IL-6R, which on the previous line is referred to as the pBS-sIL-6R-δVal-RI-NcoI. The paragraph beginning at page 30, line 10, is also consistent in this regard.

The difference between "IL-6R" and "IL-6RδVal" is explained in the paragraph beginning at page 17, line 12, of the present specification. There it states that IL-6R is produced by a cDNA encoding 468 amino acids. See, for example, GenBank record P08887, a copy of which is attached hereto. Note that the features sections of this record states that the potential extracellular region is from 20-365. Thus, the soluble form of IL-6R may go all the way up to position 365. The paragraph of the specification discussed above goes on to state that a soluble form of sIL-6R found in body fluids

has a C-terminus corresponding to Val-356, just before the transmembrane region of IL-6R. Thus, for the purpose of the preferred embodiment of the present invention, an sIL-6R sequence is used that ends at Val-356. Applicant chooses to call this sIL-6RδVal. As an applicant may be its own lexicographer, it is irrelevant how Chen defines his use of Δ. The δVal embodiment of the present invention specifically ends at Val-356.

Thus, the present specification is not ambiguous or confusing, but consistently uses the term sIL-6R when referring to the extracellular domain of the IL-6 receptor in general and uses the term sIL-6RδVal when specifically referring to the soluble IL-6 receptor that corresponds most closely to the soluble form found in body fluids and which ends at Val-356. Accordingly, claim 38 is not indefinite because the generic term sIL-6R is used in the preamble and the portion of the claim that defines which sIL-6R is being used, sIL-6RδVal is used, which is the one that ends at Val-356. In view of this explanation, reconsideration and withdrawal of this indefiniteness rejection is respectfully urged.

Claims 4, 6, 7, 9-11, 33 and 38 have been rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that

claim 38 has been amended so as to now be drawn to a narrower genus than the previous claim. The Examiner states that he is not able to find support for the limitation "which linker does not prevent the chimeric polypeptide from triggering dimerization" in conjunction with the scope of the instantly-claimed polypeptides. The Examiner states that while linkers of 3-4 amino acids are contemplated, this is in conjunction with sIL-6R/IL-6 proteins, not the δVal construct claimed herein. This rejection is respectfully traversed.

As explained above, the term sIL-6RδVal is clearly defined in the present specification. The general statement on page 7, at lines 19-21, is that the chimeric sIL-6R/IL-6 protein can use a non-immunogenic linker of about 3-4 amino acid residues. If this statement is true for the generic term sIL-6R, there is no reason why one of ordinary skill in the art would not believe that it was equally applicable to each species of sIL-6R described in the specification, and particularly sIL-6RδVal. This is not a different chimera, but a species of the generic one referred to at page 7, line 19-21. It is noted that at page 8, lines 3-6, the specific sIL-6RδVal/IL-6 is disclosed having a specific tripeptide linker. This is a species of the genus of page 7, line 19-21. Thus, the claimed statement that the sIL-6RδVal/IL-6 chimeric protein can have a linker of 3-4 amino acids is not new matter

and complies with the first paragraph of 35 USC §112, as those of ordinary skill in the art reading this section of the specification would understand that the inventors contemplated that the entire genus of sIL-6R/IL-6 proteins can have a linker of about 3-4 amino acid residues, including the preferred embodiment of sIL-6R that is sIL-6RδVal. Reconsideration and withdrawal of this rejection is therefore also respectfully urged.

Claims 6, 9-11, 33 and 38 have been rejected under 35 USC §103(a), as being unpatentable over Fischer, in view of Weich. The Examiner concedes that Fischer does not teach a 3-4 amino acid linker. However, the Exmainer states that Weich teaches fusion proteins between IL-3 and EPO using linkers either 2-3 or 23 amino acids long and that the size and flexibility of the linker does not alter the function of the chimeric protein. Thus, the Examiner considers that it would be *prima facie* obvious to one of ordinary skill in the art to make a fusion protein between the sIL-6R and IL-6 as taught by Fischer and to use a 3-4 amino acid linker with a reasonable expectation of success. This rejection is respectfully traversed.

First of all, it is noted that the Examiner has not included claim 4 in this rejection. Thus the Examiner considers the embodiment with a tripeptide linker is EFM, is

unobvious from any combination of Fischer and Weich. Since this tripeptide is unobvious, so is any other tripeptide or tetrapeptide linker. Fischer discloses that in an IL-6R/IL-6 chimera, a long linker is necessary. For this particular chimera, Fischer explicitly states in the sentence bridging pages 142 and 143, that a three-dimensional model of the complex shows that the distance between the C-terminal of IL-6R and the N-terminal of IL-6 was estimated to be in the order of 40Å . This is why Fischer used a 13 residue sequence rich in glycine and serine to connect IL-6 and IL-6R. Accordingly, one of ordinary skill in the art would consider that such a long linker was critical when making a chimera of IL-6 and its receptor.

One of ordinary skill in the art reading Weich would learn nothing to the contrary. Weich does not involve a cytokine and its receptor. IL-3 and EPO are two different cytokines. The size and flexibility of linker has different considerations when dealing with IL-3 and EPO, than when dealing with completely different linked proteins, such as a ligand-receptor pair. Weich does not disclose what the three-dimensional model shows about the optimal length of linker with IL-3 and EPO and if it did, it would have no relevance to the specific situation of IL-6 and IL-6R, which is disclosed in Fischer.

Accordingly, just as the EFM tripeptide linker of claim 4 is allowable over Fischer and Weich, so are any other tripeptide or tetrapeptide linker in view of Fischer's disclosure that because of this 40Å distance in the three-dimensional model, a longer flexible linker is necessary. The finding that only a tripeptide linker works as well as a 13 residue linker as shown in example 3 of the present specification is surprising and would not have been suggested in any way, by any combination of Fischer and Weich. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By _____
Roger L. Browdy
Registration No. 25,618

RLB:dtb
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\I\inl2\Revel15\pto\AMD 14FEB06.doc